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## *Rapid Publication*

## *Editorial*

# Can We Find Genes for Schizophrenia?

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The December issue of *Neuropsychiatric Genetics* contained an important paper by the Schizophrenia Linkage Collaborative Group for Chromosomes 3, 6 and 8 (1996) [hereafter referenced as the Collaborative Group, SLCG(1996)] on localization of genes for susceptibility to schizophrenia. The "positive," encouraging result is that they obtained support of the hypotheses that loci on chromosomes 6 and 8 have genetic variation involved in determining level of susceptibility to schizophrenia. The "negative," discouraging result is that the support falls short of confirmation ("proof") of those hypotheses and raises questions about how such proof can ever be achieved. The careful analyses and thoughtful discussion in that paper highlight several issues of relevance to future research studies both on the genetics of schizophrenia and the genetics of other neuropsychiatric disorders.

Genetic studies of schizophrenia have a long history. The generally accepted model for etiology of schizophrenia is genetic variation interacting with non-genetic variation to determine variation in liability or susceptibility to the disease. If the purely stochastic aspects of development and those aspects of "environmental" variation that are random with respect to the individual are included in the non-genetic variation, then the model becomes virtually a threshold model with total liability above a certain value being equivalent to disease. On simple additive models of variance, it is generally agreed that roughly 70% of the variation in liability in the general population is attributable to genetic variation among individuals. However, as Lewontin (1974) so clearly demonstrated over two decades ago, that numeric value itself offers very little, if any, insight into the natures of the genetic contributions, the environmental contributions, or their interactive contributions to the liability for a complex disorder like schizophrenia. When more sophisticated analytic methods began to be applied to data on patterns of familial recurrence, starting in the late 1960's, there was great hope of a clear understanding. But, complex segregation analysis, pedigree analysis, and path analysis largely failed to resolve the mode(s) of inheritance, in large part because all plausible models had many parameters and too few invariant rules, such as Mendelian transmission, to allow meaningful discrimination among alternative hypotheses. Risch (1990) did show that the pattern of recurrence risks in different categories of relatives of schizophrenic probands was inconsistent with one segregating locus and suggested multiple interacting loci, but did not pursue rigorous testing of the myriad of specific alternative hypotheses. Against that bleak picture genetic linkage studies offered hope. The advent of multiple polymorphic markers offered the possibility of knowing exactly, not just probabilistically, which segments of which chromosomes were shared by any set of relatives in any family with sufficiently complete data. The simple logic is that if sets of affected relatives almost always share some specific segment of the genome identical by descent (IBD), there can be no other explanation but that some genetic variation in that region is largely responsible for variation in susceptibility to the disorder. Linkage has been dramatically successful for Mendelian disorders but far less successful than had been expected for complex disorders, as the paper by the Collaborative Group (SLCG, 1996) makes so clear. Why is that so? Several points of general applicability to neuropsychiatric disorders, indeed to most complex disorders, are raised by the study.

The Collaborative Group study (SLCG, 1996) was designed to follow up on three previously published positive findings resulting from large-scale genome scans by individual groups: the 6p finding of Straub et al. (1995) and the 3p and 8p findings of Pulver et al. (1995). Thus, very specific prior hypotheses were being tested

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greatly simplifying (but not eliminating) the problem of significance levels. Every attempt was made to enlist collaboration irrespective of whether datasets had already been analyzed for markers in these three regions. Thus, some of the groups that had already participated in a collaborative two-stage genome scan (Moises et al., 1995) also participated in this study. The original datasets that generated the hypotheses (Straub et al., 1995; Pulver et al., 1995) were kept distinct. Finally, a limited number of specific statistical procedures were decided upon in advance. This also helped simplify the issue of statistical significance. Since the basic biological phenomenon being evaluated by all linkage methods is level of IBD of a chromosomal region among relatives with the same "abnormal" phenotype, all methods are correlated to some degree. However, the various analytical approaches make different assumptions and emphasize different aspects of the data; thus, they vary in how they evaluate both the expected and observed levels of IBD for a set of relatives and in how they evaluate the statistical significance for the difference between the two. Consequently, the more different analyses are used, the greater the chance that one will appear to give a significant result. In discussing their results the Collaborative Group make clear the problems of deciding levels of statistical significance: at what point the results are sufficiently positive that they can be accepted as proof that a region of the genome does contain relevant genetic variation. The Collaborative Group (SLCG, 1996) appears to have done everything right, and are to be congratulated for their sophisticated and thoughtful work. Unfortunately, the large data set resulting was not enough to resolve the questions of susceptibility loci on 6p and 8p. Fortunately, the new data do seem to eliminate 3p as a candidate region.

## DIRECTIONS FOR FUTURE RESEARCH

The results of the SLCG (1996) study raise serious questions about whether the approach being used to collect and analyze family material will ever be sufficient. What is wrong with the approach? There are three deficiencies in the current, state-of-the-art approaches: (1) inadequate definition of the phenotype; (2) failure to consider more sophisticated genetic models; and (3) failure to use all the genetic information in a family. Are there alternatives? Based on the growing likelihood that we have made assumptions that are too simplistic about the nature of the genetic component(s) to susceptibility to the major neuropsychiatric disorders, two general alternatives come to mind: different "kinds" of family material and different kinds of analyses. More specific thoughts on directions for future research follow in the context of those three deficiencies and the ongoing attempts to remedy them.

### Better Nosology and Diagnosis

Everyone wishes for a simple test that will identify an etiologically homogeneous subtype of schizophrenia. The history of studies of schizophrenia is replete with initially promising tests that failed and none of the current tests being studied seems especially likely to help genetic studies. In the near term hope lies elsewhere.

### More Sophisticated Genetic Models

While no one expects there to be only a single locus for schizophrenia–genetic heterogeneity is a first principle in human genetics–all linkage methods used to date focus on a single locus at a time on the expectation (hope) that "if it accounts for a high enough proportion of cases, it can be detected." But the logical construct represented by that phraseology ignores the issue of epistasis. If, as seems likely, schizophrenia is a developmental disorder (Bloom, 1993), epistasis is very likely to exist. Frankel and Schork (1996) have recently discussed some of the problems epistasis can present for linkage studies with a simple but illuminating example of a two-locus system in which neither locus has a marginal effect that would be detectable in standard linkage designs. The commentary by Frankel and Schork (1996) was motivated by studies in mice (Fijneman et al., 1996; van Wezel et al., 1996) that demonstrated epistasis by generating special backcross lines, but that alternative is not available for human studies.

Thinking from a perspective of epistasis leads in several directions. Two-locus linkage analyses need to be considered. In the abstract, two-locus linkage analyses need to consider segregation at all possible pairs of genome regions and thus require complete coverage of the genome with highly informative markers. Dizier et al. (1996) have demonstrated that individual loci in epistatic systems can be missed by standard linkage analyses. Therefore, even if a complete genome scan yields no definitive results when considered one region at a time, the data are exactly what is needed for two-locus

analyses. Also, different models of epistasis need to be considered for each pair of regions. Though the computational demands of such an approach are formidable because of the vast combinatorial possibilities, they are not beyond possibility. Moreover, exploratory analyses of much more limited hypotheses immediately come to mind. Specifically, what about epistasis involving loci in the regions of 6p and 8p that have such tantalizing hints of involvement in liability to schizophrenia? What about considering a genome scan for a second locus while "controlling for" segregation at a candidate locus like DBH that has known functional variation? The computer programs for turnkey analyses do not yet exist, but all of the components exist and the necessary data already exist for some analyses of this sort.

Another aspect of epistasis is that the marginal effects of one locus are dependent on the allele frequencies at the interacting locus or loci. The example of Frankel and Schork (1996) makes that point as does the much more elaborate epistasis model in problem 2 of the Genetics Analysis Workshop 10 (MacCluer et al., 1997; Wijsman and Amos, 1997; other papers in the same volume). Realization of that dependency reinforces the need to think in terms of population variation. Starting from a global perspective, we note that neuropsychiatric disorders appear to be present in all parts of the world. Although the epidemiology in many parts of the world may be based on older or different diagnostic criteria, the general conclusion is that the major disorders, such as schizophrenia, occur with roughly similar frequencies in all populations. However, how likely is it that the genetic factors predisposing to each disorder are the same ones at the same frequencies in all populations? While it is impossible to give a certain answer to that question, the general expectation for the global pattern of allele frequency variation can be based on studies of many loci to define the recent history of our species which was responsible for that pattern.

Few short tandem repeat polymorphisms (STRPs) have yet been studied in populations from all parts of the world, but those that have are showing an interesting pattern of many alleles in African populations, somewhat fewer in European populations, fewer still in populations in East Asia, and the fewest in the indigenous populations of the Americas and the Pacific (Bowcock et al., 1994; Deka et al., 1995; Kidd et al., unpublished). Another type of multi-allelic marker is the haplotype consisting of multiple polymorphic sites in a small segment of DNA. Some haplotypes are showing a pattern similar to that seen for STRPs: heterozygosity (diversity) is highest in sub-Saharan Africa and somewhat lower in Europe plus the Middle East, then decreases more from West to East across Asia, and finally decreases still more in the Americas (Castiglione et al., 1995; Tishkoff et al., 1996; Kidd et al., 1996). Other haplotype loci do not show such a clear picture but seem to be equally heterozygous in all populations. Still others seem to be most heterozygous in European populations, a consequence of the European bias and strong linkage disequilibrium (Kidd and Kidd, 1996; Kidd et al., unpublished). However, haplotypes at CD4 (Tishkoff et al., 1996), DM (Tishkoff et al., 1995), and DRD2 (Castiglione et al., 1995; Kidd et al., 1996) have shown something else very important: in populations outside of Africa there is very strong linkage disequilibrium across short distances (10-30 kb) at most loci and the same few chromosomes tend to be the ones found in all non-African populations. Not only is there less disequilibrium in sub-Saharan African populations, but the common haplotypes are often completely different from the common haplotypes in non-African populations. This would argue that the alleles for high susceptibility to a neuropsychiatric disorder are likely to differ in populations of sub-Saharan African origin from those in populations of European origin.

Expressed polymorphisms consisting of "normal" alleles with functional differences can also show large frequency differences among populations. Examples for genes of neuropsychiatric relevance include DRD4 (Chang et al., 1996; Chang and Kidd, 1997), DBH (Cubells et al., 1997), and CNTF (Gelernter et al., 1997). If any of these loci with functionally variant alleles were part of an epistatic system underlying susceptibility to a neuropsychiatric disorder, the allele frequency variation would be a systematic factor across populations, even populations from different parts of Europe, and the chance occurrences of genotypes within families would add noise to linkage studies of other loci and could greatly increase variation between data sets.

Thus, initial results from global studies of a few loci, some of great neuropsychiatric interest, are showing that there can be tremendous variation in allele frequencies among populations. It seems unlikely that the susceptibility to schizophrenia is the same genetically in all populations. The differences might be as simple as different proportions of the heterogeneous etiologies to as complicated as different allele frequencies at several epistatically interacting loci. Future studies need to pay closer attention to homogeneity of the sample analyzed. While it may not be a problem to restrict a study to "U.S.

whites of mixed European ancestry", it is not clear that even that will be sufficiently homogeneous.

Some of us have advocated studying large extended families with multiple affected individuals, especially families from an isolated population with a small number of founders, on the assumption (hope) that it is likely that there will be only a few of the relevant loci segregating in the population and that some disease-causing allele at one of them will have drifted to relatively high frequency. Within an extended high-density pedigree from such a population the hope is that all affected individuals have the same etiology and only one major locus is segregating. While that strategy has worked for several genetic diseases with high levels of genetic heterogeneity, such as deafness (Petit, 1996), certain warning signs are evident even for "single gene" disorders in such isolates--there can be multiple loci segregating in a single kindred (e.g. Baldwin et al., 1995) and multiple mutant alleles even if only one locus is involved (e.g. PAH, see Hoang et al., 1996). Thus, genetic homogeneity in so-called genetic isolates is often far less than previous expectations. The "genetic isolate" approach has not yet been unequivocally successful for schizophrenia but may still yield meaningful results with more powerful analytic approaches.

## Better Use of All the Genetic Information

One of the weaknesses of the Collaborative Group study (SLCG, 1996) is the reliance on pairs of affected relatives. That is not a criticism since much of the data consisted of families with only two affected individuals and most available analytic programs focus on relative pairs. However, affected sibpairs (a significant fraction of the data) have a high expectation of allele sharing by chance. Even the suggestive findings in the Collaborative Group study involve allele sharing proportions elevated, for both alleles shared, from the background of 25% to only about 30%. Thus, even assuming there is a real susceptibility locus in the region, among the pairs sharing both alleles IBD for that region of the genome, only about one pair in six actually is sharing alleles that increase susceptibility to the disorder. That gives very little help toward further progress using a bootstrapping approach of identifying subsets of patients with a more homogeneous etiology for further study. In families with pairs of affected who are more distantly related than sibs and/or with more than two affected individuals, multipoint linkage analysis has not in the past been able to consider more than one pair at a time. While not incorrect, those algorithms do not utilize all the information, especially in the more extended families. Progress has recently been made in developing programs that more fully utilize all the available data (Kruglyak et al., 1996).

One approach that may help is to focus linkage studies on families with affected relative sets (ARS), sets of three or more affected members who are distantly related (e.g., first cousins) members of an extended family. The background level of allele sharing is far lower than for pairs of siblings and the approach is apparently very powerful (Grigorenko and Chang, 1997; Schork et al., 1997; Weber and Stephenson, 1996). Though an ARS approach requires families that are less common, the added power may more than compensate for the extra effort needed to identify them.

Another analytic approach recently discussed in detail by Risch and Merikangas (1996) is fine-grained "association" studies, especially of functional variants. In fact, the approach they illustrate is a type of linkage analysis dependent upon association in the population and marker information on parents is required. They carefully note the assumptions required, such as that there be a marginal effect on phenotype of the allelic variation being studied or that the marker allele show strong disequilibrium with such allelic variation. As noted above, those assumptions will not necessarily be met in all populations. Nor will they be met if certain forms of epistasis exist. It is important to recognize that the type of "association" study Risch and Merikangas (1996) are discussing is different from the types of association study so commonly undertaken for psychiatric disorders in which only unrelated patients are studied. As discussed by Kidd (1993) and Crowe (1993) those types of association studies offer little hope of clear results. In essence, Risch and Merikangas (1996) discussed an approach that merges with linkage–the "association" exists because patients have a high level of IBD for the relevant region of the genome–in the context of a complete genome scan.

If there is an association between marker alleles and illness, other methods can be applied to extract information. The haplotype relative risk (HRR) design (Falk and Rubenstein, 1987) can be used to obtain more accurate estimates of an association because it minimizes some causes of false positive results. If an association exists, the transmission/disequilibrium test (TDT) (Spielman et al., 1993; Ewens and Spielman, 1995) can be used to test for co-transmission (i.e. linkage) of the

associated marker allele and susceptibility. These approaches involving association, however, require unambiguous identification of each allele across families. That would greatly complicate collaborations involving the data sets being assembled for linkage studies because STRP loci are involved.

The accurate identification and labeling of alleles at STRP loci can be a major problem for some types of analyses. The HRR and TDT tests noted above require consistent identification of the relevant allele. Estimates of IBD are allele-frequency dependent whenever a family is not completely genotyped and the affected pedigree method (APM) (Weeks and Lange, 1988) is always dependent on allele frequencies. Allele frequencies are poorly known for most STRP loci (most are based on only a subset of CEPH parents) and while those are not erroneous estimates, they do have very high variances. The few STRP loci that have been studied in several "European" populations (including Europe and Southwest Asia) document that significant allele frequency differences can exist among this group of populations often lumped together under the label "Caucasian." Moreover, aside from the handful of loci used in forensics, only a small minority of STRP loci has been studied in populations other than "Europeans" (Bowcock et al., 1994; Deka et al., 1995; Kidd et al., unpublished). The expectation, based on these studies and several anthropological studies individually of less global scope, is that populations from different parts of the world will have different allele frequencies. As one example, such studies predict that additional alleles and very different frequency distributions will exist in populations of African origin, such as African Americans. The Collaborative Group study (SLCG, 1996) made the reasonable assumption that alleles were consistently identified within a collaborating group and did all allele-frequency-dependent analyses within each subset of data using the frequencies estimated from that subset. They also showed that in some cases analyzed it made little difference in the final results what allele frequencies were used. Both approaches provide assurance that the results are not artifacts. However, the Collaborative Group study also noted the difficulty of identifying corresponding alleles across groups. The technical problems are such that it may be virtually impossible to combine data from different groups *post facto* for allele-frequency-dependent analyses or analyses based on association with a particular allele. Special controls will need to be decided upon before data are collected in order to assure that data can be correctly combined.

## OTHER RELEVANT STUDIES

The December issue of *Neuropsychiatric Genetics* also contained two other papers (Arolt et al., 1996; Garner et al., 1996) with data relevant to the preceding discussion of the Collaborative Group study. The Arolt et al. (1996) study is relevant to two of the points raised by the Collaborative Group: linkage to individual underlying traits rather than diagnosis and the broad region of chromosome 6 across which the positive lod scores range among the component datasets. Arolt et al. (1996) studied eye-tracking dysfunction in families with schizophrenia and did a linkage analysis of good vs. bad eye-tracking. Bad eye tracking is one of the most replicable phenotypes associated with schizophrenia, but is clearly a trait that is neither necessary nor sufficient for developing schizophrenia (e.g. Levy et al., 1993). Matthysse et al. (1986) have postulated a latent trait model to explain the association. The positive evidence for linkage obtained by Arolt et al. (1996) is quite strong, but cannot be considered proof until replications provide equally strong independent evidence. Remember that the "positive" results for bipolar disorder in the Old Order Amish reached a lod score of 4.9 in the original study (Egeland et al., 1987) but dropped dramatically with onset of illness in additional individuals and were not replicable in additional family material from the same community (Kelsoe et al., 1989). The possible identification and mapping by Arolt et al. (1996) of a locus for a trait somehow related to schizophrenia not only needs to be pursued by others but raises the interesting question of whether this hypothesized "eye-tracking" locus on chromosome 6 might be relevant to the results of the Collaborative Group. The two regions involved are about 40 cM apart (Dib et al., 1996), which is not quite independent segregation. Could segregation at this hypothetical "eye-tracking" locus be partly responsible for the very broad region of peak lod scores on chromosome 6 found for the different datasets in the Collaborative Group study? It certainly could introduce another stochastic factor that might have greater impact in some datasets than others. It is well known that changes in diagnosis of only one or two individuals in a large data set can shift the position of the maximum lod score by several centiMorgans; a loosely linked epistatic locus might cause considerable variation in the position of the lod score when a single locus is assumed for the analysis.

The Garner et al. (1996) study raises another issue.

In addition to participating in the Collaborative Group study (SLCG, 1996) they have published their own data and analyses (Garner et al., 1996). That was allowed under the rules of the collaboration (SLCG, 1996) and other groups have done/will do the same. However, the independent study by Garner et al. (1996) contains more family material than was contributed to the Collaborative Group study without indicating what fraction of the material overlaps and without separating out the analyses. Thus, it is not possible to determine the degree to which this study contributes additional independent evidence of linkage. A similar concern applies to the earlier collaborative study by Moises et al. (1995): since only some of the families were included in both studies, the degree of independent support for a 6p locus cannot be evaluated from the published studies. This is not to fault the authors in any of these cases–it is hard to think how it could be otherwise, given the complexities of collaborative studies–but serves as a warning against any meta-analyses that might be done in the future.

## CONCLUSION

We should not despair. The results for regions of 6p and 8p are sufficiently positive that it seems possible (but not certain) that they contain loci with variation affecting liability to schizophrenia. Therefore, studies of 6p and 8p need to go forward although the data are far too equivocal to warrant undertaking any attempts at cloning whatever gene(s) in the regions might be relevant. At face value, these possible genes have little overall individual contribution to susceptibility to schizophrenia but no epistatic models have yet been considered. Even if these regions prove devoid of the sought-after genes, more homogeneous data sets and more sophisticated and powerful analyses should eventually allow us to disentangle the complex genetics of schizophrenia.

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